Oxidative Stress Impairs Mitochondrial Function in Healthy and Asthmatic Primary Bronchial Epithelial Cells

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Statement of originality

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List of abbreviations:

AEC: Airway epithelial cell
AHR: airway hyper-responsiveness
APCs: antigen presenting cells
Apaf-1: apoptotic protease activating factor 1
ATCC: American type culture collection
ATP: adenosine triphosphate
BAL: bronchoalveolar lavage
BAK: BCL-2 antagonist killer
BAX: BCL-2 associated x protein
BCL-2: B-cell lymphoma
BEGM: Bronchial Epithelium Growth Medium
BHT: butylated hydroxytoluene
BSA: Bovin serum albumin
CAC: carnitine/acylcarnitine carrier
CARD: caspase recruitment domain
Cardiff: card adaptor inducing IFN-β
CAT: catalase
CBP: CREB binding protein
COPD: chronic obstructive pulmonary disease
CPT2: carnitine-palmitoyl-transferase 2
CS: Cigarette smoke
CSE: Cigarette smoke extract
DCs: dendritic cells
DMEM: Dulbecco’s Modified Eagle Medium
DMSO: dimethylsulfoxide
DNA: Deoxyribonucleic acid
DTT: Dithiothreitol
ECP: eosinophil cationic protein
EDTA: Ethylenediaminetetraacetic acid
ELISA: enzyme linked immunosorbent assay
EPO: Eosinophile peroxidise
ETC: electron transport chain
FADD: fas-associated protein with death domain
FCS/MEM: foetal calf serum/minimum essential medium
FEV: forced expiratory volumes
FVC: forced vital capacity
GCL: glutamate cysteine ligase
GM-CSF: granulocyte-monocyte colony stimulation factor
GSH: glutathione
GSHPx: glutathione peroxidise
H₂O₂: Hydrogen peroxide
HAV: hepatitis A
HCV: hepatitis C
HDL: high density lipoprotein
HSP: heat shock protein
ICAM-1: intercellular adhesion molecule-1
IFIH1: interferon-induced helicase C domain 1
IFN-γ: interferon-gamma
IL: Interleukin
IL-6: interleukin-6
IL-8: interleukin-8
IP-10: interferon-gamma inducible protein-10
IPS-1: beta promoter stimulator 1
IRES: internal ribosomal entry site
IRF3: interferon response factor 3
LDH: lactate dehydrogenase
LDL: low density lipoprotein
MAVS: mitochondrial antiviral signalling protein
MDA5: melanoma differentiation associated gene 5
MOMP: mitochondrial outer membrane permeabilization
MPO: myeloperoxidase
MPT: Mitochondrial permeability transition
mtTFA: mitochondrial transcription factor A
mtTB1: mitochondrial transcription factor B1
mtTB2: mitochondrial transcription factor B2
NF-κB: nuclear factor-κB
NHS: national health survey
NO: nitric oxide
NS: Non-structural
pBECs: Primary bronchial epithelial cells
PCR: Polymerase chain reaction
PGDF: platelet-derived growth factor
PRR: pathogen recognition receptor
RANTES: regulated on activation normal T cell expressed and secreted
RIG-I: retinoic acid-inducible gene
RIP1: receptor interacting protein1
RNS: reactive nitrogen species
ROS: reactive oxygen species
RSV: respiratory syncytial virus
RT-PCR: reverse transcription polymerase chain reaction
RV: rhinovirus
SEM: standard error of mean
SOD: superoxide dismutase
TBK1: tank binding kinase1
TCID50: tissue culture infective dose 50%
TGF-β: Transforming growth factor-β
TH1: T helper 1
TH2: T helper 2
THF: tetrahydrofuran
TLR: toll-like receptor
TNF-α: tumour necrosis factor-α
TRAF: TNF receptor associated factor
UV: Ultraviolet
VEGF: vascular endothelial growth factor
VISA: virus-induced signalling adaptor
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Abstracts (Poster presentations):


Book chapter:

Articles:

2. The effects of oxidative stress on mitochondrial function and inflammation can be reversed using lycopene and carnitine (Manuscript in preparation).
Asthma is associated with increased reactive oxidant species (ROS) in the airways which can lead to oxidative stress. A combination of several factors, such as viral infection, exposure to tobacco smoke or allergens may contribute to asthma exacerbations in the absence of effective type I and type III IFN responses. Rhinovirus infections (RVs) are associated with the majority of acute asthma exacerbations in children and adults. Mitochondria play a significant role in antiviral defence, via induction of innate immune responses through melanoma differentiation-associated gene 5 (MDA5) and mitochondrial antiviral signalling protein (MAVS) which is important for the downstream activation of type I and type III IFNs in epithelial cells. Our aims were to compare mitochondrial function and antiviral responses to RV infection in pBECs in asthmatics and healthy controls (HC) and to see whether the oxidative damage to the mitochondria can be reversed using lycopene and carnitine. Exposure of pBECs to CSE/H$_2$O$_2$ resulted in mitochondrial damage; with impaired mitochondrial membrane integrity and the co-localisation of MAVS, MDA5 and mitochondria, increased expression of mTFs, release of cytochrome-c and ATP from mitochondria which was greater in asthmatic pBECs. RV+CSE/H$_2$O$_2$ further increased mTFs and ATP release which again was exaggerated in asthmatics compared to HC. CSE and H$_2$O$_2$ had no effect on MAVS cleavage or the protein expression of MDA5, pIRF3, TBK1 and IKKɛ in both groups. Asthmatics demonstrated an impaired IFN response with, reduced CXCL-10 and IFN-λ and an increase in CXCL-8 and IL-6 release compared to HC. Also, CSE and H$_2$O$_2$ led to increased RV replication which was greater in asthmatics compared to HC. Lycopene and carnitine restored mitochondrial membrane integrity and the co-localisation between MAVS, MDA5 and mitochondria. They decreased inflammation by a marked reduction in the release of CXCL-8 and IL-6. In addition, they reduced RV replication, but did not restore CXCL-10 and IFN-λ responses.